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EXAMINER	
GOLDBERG, JEANINE ANNE	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/829,674	HELGADOTTIR, ANNA	
	Examiner	Art Unit	
	Jeanine A. Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 25-60* is/are pending in the application.

4a) Of the above claim(s) *25-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 33-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed May 3, 2006. Currently, claims 1-4, 25-29, 33-60 are pending. Claims 25-29 have been withdrawn as drawn to non-elected subject matter.

Election/Restrictions

2. Applicant's election with traverse of Group I, Claims 1-4, 33-60, namely SG13S32 allele A and SG13S114, allele T in the paper filed May 3, 2006 is acknowledged.

It is noted that Claim 2, had it not been amended to depend on Claim 1, would have been restricted from the nucleic acid detection methods and placed in its own group since it is separately classified in 435/7.1 and a separate search. In the event that a method claim requiring only a peptide analysis is presented, the claim will be subject to restriction.

The response asserts the markers and haplotypes are related insofar as they pertain to the same gene. The response further asserts the polymorphisms are located within the same FLAP nucleic acid and involve the use of polymorphisms and haplotypes to predict risk of the same disease state, susceptibility to myocardial infarction or stroke. This argument has been thoroughly reviewed but not deemed persuasive because multiple genes are related to myocardial infarction or stroke, including FLAP and phosphodiesterase 4D. Moreover, the instant specification teaches that not all of the polymorphisms are associated with myocardial infarction or stroke

(see page 83 of the specification). Thus there is no common utility. Moreover, the claims are drawn to the differences, i.e. the polymorphisms in the FLAP gene, and not the common structural features of the FLAP gene. Thus, there is no common structural feature for these polymorphisms either.

The response further asserts that the search of the claimed polymorphisms and haplotypes is not unduly burdensome. The response appears to assert that a search of SEQ ID NO: 1 is the only search required. This argument has been reviewed, but not deemed persuasive because the instant claims do not require SEQ ID NO: 1. The claims are drawn to the FLAP gene which may be any of a varity of genes. Moreover, the claims are not drawn to normal FLAP gene, but variants of the FLAP gene. Thus, a search for the normal FLAP gene would not be complete search. Furthermore, a search for each of the distinct haplotypes and polymorphisms requires a search in the literature for polymorphisms, variants, alleles etc. The polymorphic data of many genes is not placed in abstracts but rather in tables in the body of the article. Thus each article needs to be considered to provide a thorough search. It is noted that the numbering system of many of the genes is not consistent and thus provides added consideration and search for determining the presence of polymorphisms.

Claims 25-29 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement.

The requirement is still deemed proper and is therefore made FINAL.

This application contains claims 25-29 drawn to an invention nonelected with traverse in the paper filed May 3, 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Drawings

3. The drawings are acceptable.

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-2 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43

USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. With respect to claims which encompass variants, as provided in Example 11 of the Written Description Guidelines, no common structural attributes identify the members of the genus. The current claims encompass a large genus of nucleic acids which comprise variants in any region of any FLAP nucleic acid. The genus includes an enormous number of variants, polymorphisms and mutations for which no written description is provided in the specification. This large genus is represented in the specification by only the particularly named polymorphisms for which data is provided. "Polymoprhism" refers to a gene or gene product that displays modifications in sequence and/or functional properties (altered characteristics) when compared to the wild-type gene. This genus encompasses SNPs, deletions, insertions,

translocations, microsatellites, for example. The instant specification describes SNPs exclusively.

The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, variants of FLAP gene alone is insufficient to describe the genus. There is no description of the mutational sites that exist in nature and there is no description of how the structure of FLAP gene relates to the structure of any strictly neutral alleles. The general knowledge in the art concerning variants does not provide any indication of how the structure of one allele is representative of unknown alleles. The nature of alleles is such that they are variant structures, and in the present state of the art the structure of one does not provide guidance to the structure of others. The common attributes are not described. The specification provides no correlation between structure of polymorphisms and the function of such polymorphisms. The polymorphisms shown are not representative of the genus of any polymorphism associated with FLAP because it is not clear which polymorphisms within the gene (coding or non-coding) region of FLAP nucleic acid would have the same effect. One of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of only one member of this genus is not representative of the variants of the genus and is insufficient to support the claim.

Accordingly, Applicants have not adequately disclosed the relevant identifying characteristics of a representative number of species within the claimed genus.

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-4, 33-60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

<u>The nature of the invention and breadth of claims</u>

Claims 1-4, 33-60 are drawn to a method of diagnosing a susceptibility to myocardial infarction or stroke by detecting a polymorphisms or a haplotype in FLA

nucleic acid wherein the presence of the polymorphism or haplotype is indicative of susceptibility to myocardial infarction or stroke.

The nature of the invention, therefore, requires the knowledge of predictive associations between any polymorphism in any FLAP nucleic acid for any patient and susceptibility of myocardial infarction or stroke.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The art teaches the ethnicity-specific risk of myocardial infarction in the ALOX5AP or FLAP gene (see Helgadottir et al. Nature Genetics, Vol. 38, No. 1, pages 68-74, January 2006). The analysis of haplotypes illustrated three cohorts from the United States shows that HapK had varying degrees of relative risk depending on the ethnicity of the cohort. As seen in Table 1, Icelanders, Cleveland and Atlanta cohorts did not show an association with HapK with myocardial infarction (page 70).

Moreover, Meschia et al. (Ann Neurology, Vol. 58, pages 351-361, 2005) teaches that there was no evidence of association between variants of ALOX5AP and ischemic stroke. Hap A was not a risk factor for stroke in a British population but a different ALOX5AP (FLAP gene) haplotype (Hap B) was positively associated with stroke (page 351, col. 2). Meschia further continues that there was no evidence supporting linkage of either ALOX5AP or PDE4D with ischemic stroke susceptibility in these data (page 354, col. 1). As seen in Table 4 providing the analysis of ALOX5AP SNPs and association, no significant results were obtained (page 357).

The art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

Additionally, Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

The art teaches that presence of SNPs in the same gene does not indicate that each of the genes is associated with the same diseases. Meyer et al. (PG Pub 2003/0092019), for example, teaches that SNPs in the CADPKL gene are not each associated with neuropsychiatric disorders such as schizophrenia. Specifically Meyer teaches that cadpkl5 and cadpkl6 are not associated with the disease, however cadpkl7 has a p-value of less than 0.05, therefore an association exists. Each of these polymorphisms are SNPs within the CADPKL gene, however, it is apparent that they

are not all associated in the same manner with disease. Thus, Meyer exemplifies that the association of a single SNP in a gene does not indicate that all SNPs within the gene are associated with the disease.

Guidance in the Specification.

The specification provides no evidence that the skilled artisan could practice the claimed invention as broadly as claimed. The specification teaches that 49 markers were tested individually for association to the disease (page 83). Three SNPs showed nominally significant association to MI (page 83). Table 4 illustrates the nominal association of three SNPs. Further the specification concludes that "after adjusting for the number of markers tested, these results were not significant." The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied.

The claims are drawn to both polymorphisms and haplotypes. With respect to polymorphisms, the specification only teaches that of 49 markers, 3 SNPs showed nominal association. Since only 3 of 49 markers were nominally significant, it is unpredictable how to use each of the markers or any additional markers for diagnosing MI or stroke. The skilled artisan would be required to perform additional experimentation to determine how to diagnose MI or stroke using the 46 markers taught not to be associated. Moreover, while additional markers may be found in the FLAP gene, the experimentation to determine whether or not they are associated with MI or stroke is unpredictable and trial and error. It is not predictable that the polymorphisms,

whether SNPs, mutations, deletions, insertions or translocations, for example are associated with susceptibility to MI or stroke. The specification provides no correlation between structure of polymorphisms and the function of such polymorphisms with MI or stroke.

With respect to haplotypes, the instant specification provides Table 5 which is an analysis of 21 SNPs organized into haplotypes which are significantly associated with Icelandic MI patient. Table 7 illustrates 5 haplotypes over 10 SNPs which are each associated with MI. A haplotype is a combination of two or more polymorphisms. Here, while the analysis of 21 and 10 SNPs over the FLAP gene appear to provide indication of haplotypes, it is unpredictable which two, if any two polymorphisms alone may be indicative of MI or stroke. Since the specification and the art teach that polymorphisms individually are not associated with MI or stroke, but haplotypes over 21 and 10 polymorphisms are associated with MI or stroke, it is unpredictable whether two polymorphisms would provide informative guidance on whether two positions are associated with MI or stroke.

Moreover, the claims are drawn to both myocardial infarction and stroke. The specification does not appear to teach an between polymorphism association with stroke. Table 4 is directed to MI as is Table 5. The specification only analyzes the A4 haplotype with stroke. Moreover, it is noted that TIA is not significantly associated with Haplotype A4 (see page 88). Moreover as discussed above, Hap A was not a risk factor for stroke in British population (see Meschia). Thus, given the teachings in the specification and the art, it is unpredictable to associate any polymorphism or haplotype with stroke absent further unpredictable and undue experimentation. The skilled artisan would be required to perform trial and error experimentation to determine whether specific polymorphisms or haplotypes are associated with stroke. The outcome of such

research cannot be predicted and such further research and experimentation are both unpredictable and undue.

The claims are drawn to alterations in expression or composition of a polypeptide encoded by FLAP. While this claim is not entirely clear since it depends on Claim 1, Claim 2 appears to require a further detection of expression following analysis of polymorphisms or haplotypes. The instant specification nor the art teach which of the polymorphisms, haplotypes affect alterations in expression. It is unclear if these changes are even within the coding region. It is unclear whether these changes affect the protein sequence. And it is finally unclear even if the protein sequence is changed whether the expression is altered and indicative of MI or stroke. The skilled artisan would be required to perform significant further experimentation and research to determine which, if any, polymorphisms alter the protein expression. The specification does not appear to teach any polymorphisms or combinations of polymorphisms that alter the expression of a polypeptide encoded by FLAP. Further, the specification does not teach that altered expression is indicative of susceptibility to MI or stroke.

The claims are drawn to any population of individuals. The claims not only encompass humans of different ethnicities, but also different individual animals including dogs and cats, for example. The specification nor the art provide any guidance to analyzing polymorphisms in canine FLAP or feline FLAP genes to associate with susceptibility with MI or stroke. It is unclear whether these polymorphisms are conserved between mammals and whether these polymorphisms are similarly associated. Further research and experimentation which is unpredictable and undue would be required to determine whether the skilled artisan would use the claimed invention as broadly as claimed. Moreover, even within the human individuals, there is inter-ethnic variability (see Meschia and Helgadottir). The post-filing date art supports

the position that variants within different ethnicities confers different risks. It is unpredictable given the teachings in the specification directed only to Icelandic human patients and the post filing date art of Meschia and Helgadottir that all ethnicities share the same risk and ability to diagnose susceptibility to myocardial infarction or stroke.

Each of these concerns would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where there is no clear association between polymorphisms and a disorder, the broad scope of the claims may not be practiced without further unpredictable and undue experimentation. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized problems. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant -regards as the invention.

A) Claim 2 has been amended to depend on Claim 1. The new dependency is unclear. It is unclear since Claim 1 is directed to a nucleic acid detection method that Claim 2 depends on Claim 1 and is a polypeptide expression method.

Conclusion

7. No claims allowable.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

J. Goldberg

Jeanine Goldberg
Primary Examiner
July 18, 2006